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CHANGES IN ELECTROLYTE LEVELS IN UNCOMPLICATED *Plasmodium falciparum* MALARIA: THE EFFECTS OF QUININE THERAPY.

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ABSTRACT
The study was carried out to examine possible changes in electrolytes levels of outpatients with uncomplicated falciparum malaria on or without therapeutic doses of quinine sulphate with a view to highlighting possible alterations in acid-base status. A total of 40 *P. falciparum* infected patients (20 untreated and 20 treated with quinine sulphate) and 30 apparently healthy subjects (20 untreated and 10 receiving quinine for malaria chemoprophylaxis) were studied. Serum urea, creatinine, electrolytes and anion gap were determined using appropriate techniques. The result showed a significant ($P<0.05$) decrease in the levels of Na^+, Cl^- and HCO_3, while urea, creatinine with anion gap increased significantly in untreated patients compared to those of normal controls. Treatment of patients with quinine ameliorated the malaria associated changes in all parameters and restored normal acid-base status. Although the changes in electrolyte and acid-base balance of the patients were clinically mild and may not justify fluid and electrolyte supplementation, routine assessment of patients' status may assist in selection of patients with severe alterations for admission, especially when the changes persist after drug therapy.

KEYWORDS: Electrolytes, *P. falciparum*, Malaria, Quinne, Therapy.

INTRODUCTION

Plasmodium falciparum malaria is one of the most common parasitic diseases with high morbidity and mortality in tropical areas of Africa (Show *et al*,1999). The possible pathogenetic mechanisms of the infection, which results in tissue ischaemia, involves sequestration of parasitized red blood cells in microvasculature of internal organs, mainly due to cytoadherence, rosette formation and decreased deformability of the infected red cells (Row *et al*, 1997;Chen *et al*, 2000).

The clinical manifestations of falciparum malaria infection are variable and encompass a wide range of pathophysiological derangement that affect multiple organ systems including the kidney (Ehrich and Horstmann, 1985; Maitland and Marsh,2004). Severe anaemia, hypovolaemia and perturbations of electrolyte levels in African children with severe malaria have been reported (Newton *et al*,1997; Maitland *et al*, 2005). Acidosis is a common complication of severe malaria and has been identified as the single most important prognostic feature of the disease (Taylor *et al*,1993; Krishna *et al*, 1994).

Correction of fluid and electrolyte imbalance forms a major component of the treatment of severely infected malaria patients in modern intensive care settings (Hotchkiss and Karl, 2003; Maitland *et al*, 2003). This form of treatment however is not commonly considered for ambulant outpatient with uncomplicated malaria infection, possibly because severe electrolyte and fluid imbalance are least expected in such patients. But lactic acidosis, hypoglycaemia, and impaired gluconeogenesis due to limited precursor supply, were reported in patients with uncomplicated falciparum malaria (White *et al*, 1983). Moreover, treatment of severely infected malarial children on admission with quinine was associated with significantly more episodes of post-admission hypoglycaemia when compared with artermether or chloroquine (Dekker *et al*, 1997). Quinine however, remains one of the drugs of choice in the treatment of Chloroquine and sulfadoxine/pyrimethamine resistant falciparum malaria (Ache *et al*, 2002). The consequences of *Plasmodium falciparum* infection on electrolyte balance in adult out patients and especially when quinine therapy is instituted does not receive extensive consideration, although a lot has been documented on severely infected children. This study, therefore, examined the changes in electrolyte levels of uncomplicated falciparum malaria infected patients on or without quinine therapy with a view to highlighting possible alterations in acid base balance.

MATERIALS AND METHODS

Subjects and Collection of Samples

Forty malaria infected patients, aged 20-55 years, referred to Excellence Medical Diagnostic Laboratories, Aba, Abia State, Nigeria for investigations were selected for the study. Twenty of the patients which constituted the treated malaria group (MAL & QIN) had received oral 600mg quinine sulphate 8 hourly for 3 days, while the remaining 20 patients who were newly diagnosed without treatment at the time of sampling served as the untreated malaria group (MAL). Twenty apparently healthy persons of the same age range with no evidence of malaria infection served as normal control (CTR) while ten healthy persons who received similar doses of quinine sulphate for 3 days for malaria chemoprophylaxis served as treated control (CTR + QIN).

Malaria parasitaemia was determined by microscopic examination of Giemsa stained thick blood film for the presence of parasite-infected red cells.

Five milliliters of blood was collected by venipunture from each participant, dispensed into screw-caped plain sample tube and allowed to clot and retract at room temperature 22 – 27^0C for 2 h. The sera were separated, after centrifuging at 3000 rpm for 5 min in clinical bench top centrifuge (MSE Minor England) using pasteur pipettes.

The sera were store in a refrigerator at 2-8^0C until required for analysis, which was done within 24 h.

Determination of Serum Urea

Serum urea was determined by the Fearon reaction method (DiGiorgio, 1974) in which urea react with diacetyl monoxime to form yellow diazine derivative. The intensity of the colour measured at 520nm was directly proportional to the concentration of urea in the sample.

Determination of Serum Creatinine.

Serum creatinine was determined by the Jaffe reaction method (Narayanan and Appleton, 1980). Protein present in 0.5ml of serum was precipitated with 0.5ml of sodium tungstate and centrifuged at 3000rpm for 5 min. Creatinine present in 0.8ml of the supernatant was reacted with 0.5ml of alkaline picrate to form a red complex whose absorbance was read in a spectrophotometer at 520nm against reagent blank after 15 min incubation at room temperature (22-27^0C).

Electrolyte Assays

The serum concentrations of sodium, potassium and chloride ions were determined by colourimetric methods using reagent kits from Teco Diagnostics, Anaheim, U.S.A. The absorbances of all tests were read in a spectrophotometer (HAICH, DR 3000, Germany), and all the assay procedures were according to the kit manufacturers instruction.

Sodium was determined by the modified method of Maruna (1958). Sodium was precipitated as sodium magnesium uranyl acetate. The excess of uranium was reacted with ferrocyanide to produce a chromophore whose absorbance at 550nm was inversely proportional to the concentration of sodium in the serum sample.

Potassium was determined by direct measurement of absorbance at 500nm of a colloidal suspension formed when potassium in serum sample mixes with sodium tetraphenylboron. The turbidity of the solution was directly proportional to the concentration of potassium in the sample.

Chloride ion concentration was determined by the modified method of Skeggs and Hochestrasser (1964). Chloride ions formed a soluble, non-ionized, compound with mercuric thiocyanate. The released thiocyanate ions react with ferric ions to form a red coloured complex, which was read colourimetrically at 480nm.

Serum bicarbonate ion concentration was determined by titrimetric method (Hodes, 1953). 1ml of 0.01N hydrochloric acid was added to a fresh dilute serum sample. Shaking the sample thoroughly expelled the carbon dioxide formed. The hydrogen ions that remained were titrated against 0.01N sodium hydroxide using two drops of phenol red until a pink end point was obtained. The concentration of bicarbonate ion in serum was calculated.

Statistical Analysis

Data are presented as mean ± SD. The differences between groups were tested using students' t-test. A probability of 0.05 was chosen as a level of significance.

RESULTS

The mean ages, urea and creatinine concentrations of malaria infected patients on or without quinine therapy are presented in table 1. The mean ages of all the groups were not significantly different. Serum urea and creatinine concentrations in untreated malaria patients were significantly ($P<0.05$) higher than those of normal control and quinine treatment healthy subjects. However, the urea and creatinine levels in quinine treated malaria infected patients were not significantly different ($P<0.05$) from those of controls.

The concentrations of sodium, chloride and bicarbonate ions were significantly lower ($P<0.05$), while the potassium ion and anion gap were significantly higher, in untreated malaria patients when compared with those of normal control subjects (Table 2). The percentage decrease in Na^+, Cl^- and HCO_3^- of untreated malaria infected patients from normal control values were 12.2%, 13.4% and 40.6% respectively while K^+ and anion gap were 22.5% and 31.7% higher than normal values respectively. Changes in these parameters were ameliorated by treatment with quinine sulphate.

DISCUSSION

Correction of fluid volume and electrolyte deficits has been the standard of care for any critically ill patients including those with severe falciparum malaria infection. This is because acidaemia, hypokalaemia, hypocalcaemia and hyponatraemia exacerbate myocardial dysfunction and increase the risk of arrhythmias (Khilnami, 1992; Kumar *et al*, 2001). In Africa, particularly in Nigeria where malaria is endemic, many adults might have developed partial immunity against malaria and are less likely to become critically ill when infected. This set of patients presents at the out patient department of hospitals or clinics, and are not commonly considered for fluid volume and electrolyte deficit correction, possibly because severe electrolyte and fluid imbalance are rarely expected. We have observed mild hyponatraemia, hyperkalaemia and acidosis in the adult falciparum malaria infected patients. Malaria infection is characterized by fever, sweating and increased catabolism of protein and glucose, which result in increased circulation of lactic acid (Miller, 1985).

The decrease in concentration of sodium may be due to losses in sweat and urine. Losses in urine may serve to compensate for increased lactate and urea concentrations found commonly in falciparum malaria infection, in order to maintain constant body osmolality. Reduction of sodium concentration by increased urea, alcohols and other osmotically active solutes have been considered appropriate if constant osmotic gradient between cells and the extra-cellular fluid compartment is maintained (Mayne, 1994). Our findings is in line with the report of hyponatraemia and hyperkalaemia in patients infected with *Plasmodium falciparum* (Olaniyan, 2005), but however contrast with hypokalaemia reported in 27.3% of Indians admitted for severe falciparum malaria infected with evidence of severe renal derangement (Nand *et al*, 2001).

Metabolic acidosis is associated with hyperkalaemia because increased hydrogen ions are available for sodium exchange in the renal tubules at the expense of potassium ions and hence result in increase retention of potassium in serum. Furthermore, increased urea:creatinine ratio in these patients suggests that the ureamia observed in this study is largely prerenal and may be due to reduced renal blood flow and glomerular filtration rather than organic renal involvement. Impaired glomerular filtration amidst hyponatraemia reduces the amount of sodium ions available in the renal tubule for potassium exchange and therefore contribute to the elevation of serum potassium concentration. Acidosis, as evident by increased anion gap and reduced bicarbonate ion concentration, in the malaria patients may be the result of increased anaerobic catabolism of glucose with subsequent generation of large amount of lattice acid (Krishna et al, 1994). Administration of quinine sulphate to the patients ameliorated the malaria associated perturbations in electrolytes and acid-base balance. The mechanism for this restoration by quinine in the patients is not fully understood but may be associated with enhanced destruction and eradication of malaria parasites from the body. Also, quinine-induced increase in insulin secretion (Doyle and Egan, 2003) may contribute to the observed reduction in potassium levels following treatment of malaria infection. Insulin is known to enhance cellular uptake of potassium along with glucose from the extracellular fluid compartment and hence may reduce its serum concentration (Mayne, 1994). We observed a non-significant decrease in serum concentration of potassium in healthy subjects treated with oral quinine in this study. Intravenous quinine administration on healthy fasting volunteers had also been shown

to increase their mean plasma insulin level, which correlated positively with the plasma quinine concentration (white *et al*, 1983).

Although, the degree of hyponatraemia, hyperkalaemia and acidosis in patients with uncomplicated falciparum malaria were mild and may not justify the provision of routine supplementation except where the changes persist after drug treatments, information on the electrolyte and acid-base status of patients may be useful in making management decisions for those who may develop complications.

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Table 1: Ages, urea and creatinine concentrations of malaria infected patients on or without quinine treatment

Group	Age (years)	Urea (mmol/L)	Creatinine (µmol/L	Urea:creatinine Ratio
CONTROL	29.6 ±6.24	3.52± 0.53	97.35±22.3	19.18±3.18
CTR + QIN	28.1±5.23	3.40±0.63	92.04±27.44	19.62±2.93
MAL	30.3±3.91	7.23±0.82*	131.87±21.24*	29.73±4.31*
MAL + QIN	27.1±4.45	3.47±0.95**	96.47±31.86**	19.08±3.23**

* Significant difference when compared with CTR at P<0.05
** Significant difference when compared with MAL at P<0.05
CTR =Normal control subjects; CTR + QIN = Normal subjects taking quinine treatment; MAL = Malaria infected patients without treatment; MAL + QIN = Malaria patients taking quinine treatment.

Table 2: Electrolyte levels of malaria infected patients on or without quinine treatment.

Group	Electrolyte (mmol/L)				Anion gap
	Na^+	K^+	Cl^-	$HC0_3^-$	(mmol/L)
CTR	139.80± 10.38	3.83± 0.18	97.90± 11.13	27.60± 3.71	18.13±2.15
CTR+QIN	134.80 ± 9.00	3.23± 0.49	94.20± 8.39	26.70 ±6.11	17.13±3.22
MAL	122.80±* 9.94	4.94±* 0.27	84.80* ±6.6.42	16.40 ±2.89*	26.54±2.31*
MAL+QIN	138.10±** 4.88	3.56±** 0.46	97.10 ±4.53	24.80** ±3.45	19.76±2.62**

* Significant at $p<0.05$ when compared with CTR

** Significant at $p<0.05$ when compared with MAL

CTR =Normal control subjects; CTR + QIN = Normal subjects taking quinine treatment; MAL = Malaria infected patients without treatment; MAL + QIN = Malaria patients taking quinine treatment.

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